REMARKS

According to the Action, Claims 1, 5-15 and 49 were examined, the remaining claims having been withdraws as a result of a Restriction Requirement.

Applicants thank Examiners Blanchard and Helms for the courtesy of a telephonic interview conducted on April 15, 2005, which is referred to at various points below.

Claims 1, 4, 5, 7, 11-13 and 49 have been amended in response to the Office Action or, in a few cases, voluntarily to increase clarity. Some of these amendments reduce the number of dependencies. Claim 6 is being cancelled.

New claims 52-57 have been added. As noted below, Claims 52-55 correspond to part of claims 5, 11 12 and 49, respectively, and now depend only from withdrawn claims 3 and 4. This is done in the likelihood, based on the interview, that claims 3 and 4 will be rejoined.

Claims 56 and 57 are directed to an embodiment of an N-terminal fragment of the H/P domains of HPRG that are closely tailored around the (H,P)-(H,P)-P-H-G consensus sequence that abounds in the N-terminal segments of the human and rabbit H/P domain sequences. Support for these claims can be found at page 16, line 26, where it is stated that "a preferred peptide comprises a minimal consensus sequence [H/P][H/P]PHG (SEQ ID NO:7)" and in the disclosure elsewhere of multimers of the consensus sequence.

Withdrawn claims 3 and 4 are being amended for increased clarity, to emphasize the requirement that the ligand binding and biological activity be similar to that of HPRG and the H/P domains thereof.

Applicants' claim count indicates that no additional "extra claim" fees are due because the reduction in the number of claims due to canceled dependencies or canceled claims equals or exceeds the number of new claims.

The after-filing publication (by the present inventors and their colleagues - Doñate *et al.*, 2004) verifies the biological and binding activity of (H,P)-(H,P)-P-H-G pentapeptides, as disclosed in the specification and certain variants thereof. One of the "lessons" of this paper is that apart from the expected effects of conservative substitutions, an alanine scanning mutagenesis approach to the (H,P)-(H,P)-P-H-G pentapeptide, specifically, the HHPHG sequence showed that a "small-for-basic" residue substitution also preserved bioactivity of parent peptides.

Claims 1, 2, 5-15 and 49 are now active in this case. It is submitted that no new matter has been introduced by the present amendments and entry of the same is respectfully requested. Applicants respectfully submit that their application is now in condition for allowance.

I. *Election/Restrictions*

The Office Action notes that Applicant elected with traverse of Group 1, claims 1, 5-6, 11-15 and 49 in part and claims 7-10 and requested withdrawal of the Restriction requirement between Groups 1 and 2. This was granted. The Examiner thus examined Claims 1, 5-15 and 49 to the extent that the polypeptide or peptide comprise a human HPRG (SEQ ID NO:5) or rabbit HPRG (SEQ ID NO: 6) (*i.e.*, to the exclusion of claims directed to peptide multimers (claims 3 and 4, and various claims dependent thereon). . Claims 2-4, 16-48 and 50-51 were withdrawn from further consideration pursuant as being drawn to a nonelected invention.

During the interview, Applicant noted that both the Office and Applicant apparently overlooked the fact that claim 2 should have been included with Group 1. Claim 2 is a subgenus of claim 1(d) that selects three of the four possible sequences of SEQ ID NO:7. The Examiner indicated that this claim had, in fact, been searched and that it would be considered part of the elected invention and not withdrawn. Applicants are therefore treating claim 2 as a pending claim herein.

Applicants also note that it is their understanding from the substance of the interview that the peptide multimer claims (3 and 4) would be considered for rejoinder when the Office examines the present response, due in part to the similarity of some of these multimers to embodiments included in claim 1(d) and the additional support of the after-filing publication submitted herewith.

II. Claim Objections

Claims 1, 5-7, 11-12 and 49 were objected to because they also include non-elected inventions. Applicants do not understand why claim 1 falls in this category. Any dependent claims that carried along a dependence from claims 3 and 4 have been amended to delete such dependence. On the other hand, in view of possible rejoinder of claims 3 and 4, Applicants are submitting new claims 52-55 (that parallel original claims 5, 11 12 and 49, respectively, but now depend only from claims 3 and 4) to be considered together with the rejoinder of claims 3 and 4.

III. Rejections Under 35 U.S.C. § 112, Second Paragraph

Several grounds for rejection for indefiniteness were asserted. These are briefly indicated below. The present amendments correct the underlying typographical or other errors, mooting this ground for rejection so that this rejection may properly be withdrawn

A. Claims 1 and its dependent claims were considered indefinite due to the language "human rabbit HPRG" in claim 1. This was a typographical error; claim 1(b) now reads "rabbit HPRG".

B. Claims 11 and 12 reciting "therapeutically effective amount" in claiming a pharmaceutical composition. This errant phrase was deleted.

IV. Rejections Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 1, 5-15 and 49 were rejected for allegedly failing to comply with the written description requirement. The Action states that there is insufficient written description of what can be

> ...a sequence variant of SEQ ID NO:5 or SEQ ID NO:6 having substantially the same biologic activity of inhibiting angiogenesis, endothelial cell proliferation or endothelial tube formation...

The Action asserts that the relevant identifying characteristics of the genus such as structure or other physical and/or chemical characteristics of "a sequence variant of SEQ ID N0:5 or SEQ ID NO:6" are not described in the application in a manner commensurate in scope with the claimed invention (citing *Vas-Cath Inc. v. Mahurkar,* 19 USPQ2d 1111; *Fiers v. Revel,* 25 USPQ2d 1601, 1606; *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 ; *Fiddes v. Baird,* 30 USPQ2d 1481, 1483; and "The Enzo Case" (presumably, Enzo Biochem, Inc. v. Gen-Probe Inc., 285 62 USPQ2d (BNA) 1289 vacated by 63 USPQ2d 1609) (Fed. Cir. 2002)).

B. Applicants' Response

This rejection was discussed at length during the interview, to some degree in conjunction with the related enablement/scope rejections (see below). Applicants have amended claim 1 to require in part (c) that the sequence variants of SEQ ID NO:5 and NO:6 now claimed are conservative amino acid substitution variants having substantially the same ligand binding activity or biologic activities of the native H/P domains described by these sequences.

Amino acid substitution and addition variants are discussed at page 19, line 19 to page 20 line 10 of the specification and conservative substitutions "within groups" are indicated. In general,

this concept is well-known in the art. The classical "basic" residues of Arg and Lys are known to be substitutable for His, which is a frequent residue in the presently claimed polypeptide domains and shorter peptides.

Applicants do not agree with the Office's analysis of the written description requirement as regards their claims and believe that the specification does provide adequate written description for the claims as filed and as preliminarily amended. Nevertheless, to advance this case to allowance, they have made the indicated amendments to claim 1.

Based on Applicants' understanding of the Office's position after conducting the interview, they believe this ground for rejection should and will and be withdrawn.

V. Rejection Under 35 U.S.C. § 112, First Paragraph - Lack of Enablement

A. The Rejection

The Office has rejected Claims 1, 5-15 and 49 for lack of enablement. The specification allegedly does enable sequence variants of human HPRG or sequence variants of rabbit HPRG (or an affinity ligand for binding to or isolating human HPRG sequence variants or rabbit HPRG sequence variants). The Office cited the eight "Wands Factors" (*In re Wands,* 8 USPQ2d 1400, 1404 (Fed. Cir. *1988).*)

As characterized by the Office, the claims are drawn to an isolated anti-angiogenic polypeptide or peptide having the H/P domain of human HPRG (SEQ ID NO:5) or the H/P domain of rabbit HPRG (SEQ ID NO:6) and sequence variants thereof, which broadly encompasses analogs, derivatives, fragments, and homologs of the human HPRG and rabbit HPRG, wherein the polypeptide or peptide or sequence variant is diagnostically or therapeutically labeled. The claims are also drawn to an affinity ligand useful for binding to or isolating a human HPRG or rabbit HPRG or sequence variant thereof.

The Office asserts that the disclosure in the specification, e.g., human and rabbit HPRG sequences (pages 11-14) HPRG and the H/P domains that inhibit angiogenesis (Examples), that that fragments, analogs, or derivatives of the HPRG polypeptide would be amenable to functionally equivalent amino acid substitutions (pages 19-23). The Office takes the position that the foregoing does not provide specific guidance that would enable one skilled in the art to make and use the invention without undue experimentation.

Also noted is that the specification allegedly does not disclose the extremely large number of proteins broadly encompassed by the claims, which encompass a significant number of inoperative

species among the analogues, derivatives, fragments or homologues. The Office provided a number of highly selected references that show how substitutions have a major impact on protein function.

B. Applicants' Response

During the interview, Applicants discussed various aspects of the enablement analysis with the Examiner, pointing out the advanced state of the art for making, and identifying a large number of variants (either randomly or selectively) and the high throughput methods for screening them for the appropriate and recited binding or biological activity without such efforts being "undue experimentation."

Applicants understood from the Examiner that this enablement rejection would be reviewed and removed if the claim was limited to "conservative substitution variants," as it has been, in light of the advanced state of the art in 2001 and the disclosure in the specification. . Therefore, despite the fact that Applicants still disagree with the Office over a number of the aspects of its enablement analysis and rejections, it is believed that a detailed discussion of these points would not be of benefit here. Applicants believe, based on statements made during the interview, that their amendment of claim 1(c) (along with their addition to claim 1(d) of the functional limitations already present in original claim 1(c), would satisfy the Office that the claims are now fully enabled by the specification coupled with the state of the art. Hence, Applicants request that this ground for rejection be withdrawn.

VI. Rejections Under § 102

Many of the rejections under §102(b) or (e) are due to the fact that claim 1 was interpreted as reading on the full length human or rabbit HPRG protein (SEQ ID NO:1 and SEQ ID NO:3). Applicants were well aware of the art disclosing the whole protein and did not intend to cover it in their claims. It was the Office's interpretation of the term "having" as equaling "comprising" in claim 1, that resulted in the claim unintentionally reading on the whole protein. This has been remedied as is discussed below.

In contrast, Applicants believe that they are the first to discover certain properties of this protein (as well as its domains and shorter peptides from the domains), namely, the anti-angiogenic activity. Therefore, Applicants believe that certain method claims involving use of the full length protein (as well as a domain, fragments and pentapeptides) are patentable over the same cited art. However, because those method claims are presently withdrawn pursuant to a restriction

requirement, this issue will not be discussed here. Because of the rejoinder rules under *In re Ochiai*, Applicants will only seek ultimate rejoinder in this application of method claims that correspond in scope to the composition claims. Any additional or broader method claims will await the filing of a divisional or other continuation application claiming priority from the present case. Withdrawn method claim 23 and 24, for example, depend from claim 11 and back to claim 1, and therefore, have the same scope as the composition claims being examined presently.

Discussion of the cited reference and specific rejections follow.

A. § 102(b) Rejection over Koide

Claim 1 was rejected as anticipated by Koide *et al., Biochemistry, 25*:2220-2225, 1986 ("Koide") this is because the Office construes the term "having the sequence of" as "comprising." Under this construction, claim 1 directed to domains or peptides of human or rabbit HPRG are said to read on the full length proteins. Koide discloses the human HPRG polypeptide, "which comprises a sequence that is identical to SEQ ID NO:5."

During the interview, Applicant discussed various options to narrow this claim language, including amendment of the transitional phrase. Applicants have elected instead to narrow the claim by excluding by proviso the full length human and rabbit HPRG protein/polypeptide from the scope of the claim. This is believed to be adequate to distinguish from Koide.

B. §102(b) Rejection over Borza

Claims 1, 11, 13 and 49 are rejected as being anticipated by Borza *et al.* (*Biochemistry 35*:1925-1934, 1996 ("Borza"), which is said to teach rabbit HPRG polypeptide (having a sequence identical to SEQ ID NO:6). The reference is also said to teach human HPRG polypeptide (Figure 2). Additionally, Borza is also a basis for rejecting the pharmaceutical composition claims since, according to the Office, the disclosure of rabbit HPRG polypeptide in 0.1 M sodium phosphate buffer, pH 7.4, which is interpreted to be a pharmaceutically acceptable carrier and in form suitable for injection. Borza discloses rabbit HPRG bound to a DEAE-cellulose column which is said to anticipate claim 49 to an affinity ligand useful for binding to or isolating an HPRG-binding molecule.

As discussed in Section A, above, the present amendment of claim 1 is believe to distinguish from each of these teachings of a full length HPRG polypeptide. Thus, the amended claims are believed to be patentable over Borza.

C. §102(e) Rejection over Simantov

Claims 1, 5-15 and 49 are rejected as being anticipated by Simantov *et al.* (US 2001/0041670 Al, 12/6/1999; "Simantov") which allegedly also discloses human HPRG protein, pharmaceutical compositions comprising the protein, and diagnostically or therapeutically labeled HPRG protein.

As discussed in Sections A and B above, the amendments to claim 1 *et seq.* are believed to distinguish from this reference.

D. § 102(e) rejection over Olsson

Claims 1, 5-15 and 49 are rejected as being anticipated by Olsson A-K *et al.* (US 2002/0165131A1, 2/5/2001; "Olsson"). This document is said to teach an anti-angiogenic pharmaceutical composition comprising a rabbit or human HPRG polypeptide and a pharmaceutically acceptable carrier. The polypeptides are said to have the H/P domain of human or rabbit HPRG (present SEQ ID Nos:5 and 6, respectively). The reference allegedly teach that the HPRG polypeptides may be coupled to (a) diagnostic or therapeutic moieties including radionuclides, fluorescein, rhodamine and others, or (b) solid supports/affinity columns for the isolation of the HPRG receptor (an affinity ligand for binding to or isolating an HPRG-binding molecule") (see page 7, paragraph P070). Thus, Olsson *et al.* anticipate the claims.

The amendments already discussed above distinguish the present claims in part from the Olssen disclosure, as they do to the other cited documents (Sec's. A-C, above).

More importantly, Applicants submit herewith a **Rule 131 Declaration** of co-inventor Fernando Doñate showing notebook pages that support a date of invention prior to the earliest priority date of the published Olssen patent application, **January 05, 2001**. Therefore it would be proper to remove this reference as prior art for all its cited teachings.

VII. CONCLUSION

In conclusion, it is respectfully requested that the above amendments, remarks and requests be considered and entered. Applicant respectfully submits that all the present claims are free of the cited prior art, in compliance with 35 U.S.C. § 112, and therefore in condition for allowance, and respectfully requests early notice of such favorable action.

Examiner Blanchard is respectfully requested to contact the undersigned at (202) 496-7845 with any questions or comments if they will assist in the understanding this amendment and response.

If these papers are not considered timely filed by the Patent and Trademark Office, then a petition is hereby made under 37 C.F.R. § 1.136, and any additional fees required under 37 C.F.R. § 1.136 for any necessary extension of time, or any other fees required to complete the filing of this response, may be charged to Deposit Account No. 50-0911. Please credit any overpayment to deposit Account No. 50-0911.

Respectfully submitted,

Dated: April 18, 2005

By_____

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